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Relationship of body mass index with efficacy of exenatide twice daily added to insulin glargine in patients with type 2 diabetes

This *post hoc* analysis assessed the evidence behind common reimbursement practices by evaluating the relationship of body mass index (BMI) ranges (<30, 30–35 and >35 kg/m^2) with treatment effects of exenatide twice daily among patients with type 2 diabetes. Patients received exenatide twice daily added to insulin glargine in two 30-week studies (exenatide twice daily vs insulin lispro, n = 627; exenatide twice daily vs placebo, n = 259). No association of baseline BMI with changes in efficacy variables was observed. Glycated haemoglobin (HbA1c) reductions were significant ($p < 0.0001$) and similar across BMI range groups in the lispro-comparator study and greater for exenatide versus placebo in the placebo-controlled study. Significant weight loss occurred with exenatide across BMI range groups ($p < 0.0001$), while weight increased with both comparators. Achievement of HbA1c <7.0% (<53 mmol/mol) without weight gain was greater for exenatide versus comparators. Systolic blood pressure decreased across BMI range groups with exenatide in the lispro-comparator study ($p < 0.0001$); changes in lipids were not clinically meaningful. Minor hypoglycaemia was less frequent for exenatide versus insulin lispro. These findings suggest that BMI alone should not limit clinical decision-making or patient access to medication.
Keywords: body mass index, exenatide twice daily, type 2 diabetes

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RESEARCH LETTER

Introduction

Type 2 diabetes (T2D) is a progressive disease requiring stepwise treatment intensification to maintain glycaemic control [1]. Recently, we reported that adding the short-acting glucagon-like peptide-1 receptor agonist (GLP-1RA) exenatide twice daily to basal insulin improved glycaemic control similarly to the addition of mealtime (three times daily) insulin lispro to basal insulin, but with less non-nocturnal hypoglycaemia, weight loss, reduced systolic blood pressure (SBP) and improved quality of life [2]. Additional studies have reported beneficial effects of the combination of a GLP-1RA and insulin [3,4]. Accordingly, recent international guidelines have included the addition of a GLP-1RA to background basal insulin as an option for patients requiring combination injectable treatments [1]. However, several countries restrict reimbursement of GLP-1RAs to only patients with a body mass index (BMI) ≥35 kg/m^2 [5,6].

In the present *post hoc* analysis, we assessed the evidence behind common reimbursement practices by evaluating the relationship of standard BMI ranges with the effects of exenatide twice daily among patients with T2D treated with insulin glargine in two 30-week studies.

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Materials and Methods

Study Design and Patients

This *post hoc* analysis included two open-label, randomized, non-inferiority studies that were published previously [2,7]. The lispro-comparator study (NCT00960661) investigated the efficacy and safety of exenatide twice daily versus insulin lispro added to background insulin glargine and metformin, after a basal insulin optimization phase in which bedtime insulin glargine was titrated based on self-monitored blood glucose. The placebo-controlled study (NCT00765817) investigated the efficacy and safety of exenatide twice daily versus placebo when added to background insulin glargine, with or without metformin and/or pioglitazone. Detailed methods of both studies have been described previously [2,7], and study procedures are shown in Figure S1, Supporting Information. The exenatide dose was 5 µg twice daily for the first 4 weeks and 10 µg twice daily thereafter, given before breakfast and dinner.

The protocol for each study was approved by an institutional review board, and both studies were conducted in accordance with the principles described in the Declaration of Helsinki. All patients provided written informed consent.

Statistical Analyses

The primary objective was to compare the changes from baseline in efficacy and safety measures with add-on exenatide twice daily versus insulin lispro or placebo for three groups with standard ranges of baseline BMI (<30, 30–35 and >35 kg/m^2) [8,9] in the intention-to-treat (ITT) population,

Table 1. Baseline characteristics by baseline BMI range group (intention-to-treat population).

Lispro-comparator study characteristics	Exenatide twice daily <30 kg/m² n = 107	Exenatide twice daily 30–35 kg/m² n = 120	Exenatide twice daily >35 kg/m² n = 88	Insulin lispro <30 kg/m² n = 113	Insulin lispro 30–35 kg/m² n = 111	Insulin lispro >35 kg/m² n = 88
Male, n (%)	68 (63.6)	52 (43.3)	35 (39.8)	55 (48.7)	62 (55.9)	41 (46.6)
Age, years	61.8 (9.2)	59.0 (10.2)	59.1 (8.6)	59.0 (9.5)	60.8 (9.2)	59.0 (9.7)
Body weight, kg	77.0 (9.6)	89.5 (11.5)	106.1 (15.4)	76.3 (10.6)	90.0 (12.0)	105.0 (16.5)
BMI, kg/m²	27.3 (1.7)	32.4 (1.4)	38.7 (2.5)	27.6 (1.7)	32.1 (1.3)	38.4 (2.6)
HbA1c, mmol/mol	65 (9.5)	68 (11.1)	68 (11.6)	65 (9.1)	66 (9.6)	68 (10.1)
FPG, mmol/l	6.4 (2.0)	7.5 (2.6)	7.5 (2.3)	6.4 (2.3)	7.4 (2.5)	7.3 (2.7)
SBP, mmHg	135.6 (14.5)	136.6 (16.3)	140.0 (16.3)	130.9 (15.9)	134.9 (15.1)	137.9 (14.4)
DBP, mmHg	75.9 (9.5)	79.9 (8.5)	81.7 (10.3)	76.0 (9.3)	78.4 (8.5)	80.7 (9.2)
LDL cholesterol, mmol/l	2.48 (0.92)	2.53 (0.86)	2.58 (0.83)	2.63 (0.88)	2.51 (0.89)	2.66 (0.90)
HDL cholesterol, mmol/l	1.29 (0.38)	1.21 (0.32)	1.19 (0.27)	1.26 (0.32)	1.14 (0.32)	1.20 (0.31)
Total cholesterol, mmol/l	4.55 (1.1)	4.57 (1.0)	4.61 (0.95)	4.63 (0.99)	4.48 (1.13)	4.68 (0.99)
Triglycerides, mmol/l, median (range)	1.49 (0.50, 5.97)	1.59 (0.51, 9.13)	1.65 (0.61, 7.57)	1.45 (0.67, 5.54)	1.48 (0.57, 8.64)	1.60 (0.60, 5.73)
Placebo-controlled study characteristics	**Exenatide twice daily <30 kg/m² n = 36**	**Exenatide twice daily 30–35 kg/m² n = 50**	**Exenatide twice daily >35 kg/m² n = 51**	**Placebo <30 kg/m² n = 43**	**Placebo 30–35 kg/m² n = 35**	**Placebo >35 kg/m² n = 44**
Male, n (%)	19 (52.8)	32 (64.0)	19 (37.3)	32 (74.4)	22 (62.9)	24 (54.5)
Age, years	62.2 (8.7)	57.7 (9.5)	55.5 (7.5)	60.3 (12.0)	59.5 (7.7)	56.7 (9.1)
Body weight, kg	73.7 (12.8)	94.6 (11.4)	111.4 (17.1)	75.6 (12.8)	89.7 (11.3)	113.4 (16.2)
BMI, kg/m²	26.8 (2.6)	32.7 (1.4)	39.9 (3.2)	26.9 (2.6)	32.3 (1.3)	39.7 (3.9)
HbA1c, mmol/mol	67 (8.0)	66 (8.6)	69 (10.5)	69 (11.0)	70 (10.5)	70 (10.2)
FPG, mmol/l	7.2 (2.8)	7.2 (2.1)	7.5 (2.8)	6.6 (2.2)	7.8 (3.3)	8.0 (2.4)
SBP, mmHg	129.8 (15.0)	128.4 (15.5)	131.4 (17.4)	126.4 (12.3)	126.6 (13.7)	129.5 (15.1)
DBP, mmHg	71.5 (8.1)	75.5 (8.5)	79.0 (10.7)	72.7 (7.9)	74.0 (10.6)	76.2 (7.9)
LDL cholesterol, mmol/l	2.61 (0.95)	2.32 (0.93)	2.55 (0.92)	2.31 (0.69)	2.43 (0.83)	2.55 (1.05)
HDL cholesterol, mmol/l	1.20 (0.30)	1.12 (0.29)	1.13 (0.24)	1.19 (0.31)	1.13 (0.29)	1.09 (0.30)
Total cholesterol, mmol/l	4.57 (1.10)	4.22 (1.07)	4.55 (1.09)	4.12 (0.88)	4.34 (0.90)	4.43 (1.17)
Triglycerides, mmol/l, median (range)	1.40 (0.45, 5.68)	1.49 (0.59, 5.31)	1.83 (0.45, 5.57)	1.27 (0.46, 3.79)	1.50 (0.73, 4.03)	1.46 (0.80, 3.63)

Data are mean (standard deviation) unless otherwise stated. BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; SBP, systolic blood pressure.

defined as all randomized patients who received ≥1 dose of study drug.

Efficacy measures included glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, blood pressure (BP), LDL cholesterol, HDL cholesterol, LDL cholesterol/HDL cholesterol ratio, total cholesterol, triglycerides, and achievement of HbA1c <7.0% (<53 mmol/mol) and HbA1c <7.0% with no weight gain. Changes in BP and lipids were determined for patients in each BMI range group who did not add new antihypertensive or lipid-lowering medication, respectively. Safety measures included the incidence of treatment-emergent adverse events (TEAEs) and minor and major hypoglycaemia.

Baseline demographics, TEAEs, hypoglycaemia rates and goal achievement were summarized by descriptive statistics. Changes from baseline to endpoint in efficacy variables were evaluated with the last observation carried forward method and analysed with an analysis of covariance model, in which the baseline value of the dependent variable was adjusted as a covariate. The relationship of baseline BMI to the change from baseline to endpoint in efficacy variables was examined, and the Pearson correlation coefficients (r) were provided.

Results

Study Population

A total of 627 of 637 randomized patients in the lispro-comparator study and 259 of 261 randomized patients in the placebo-controlled study received ≥1 dose of study medication after randomization and were included in this analysis. Mean baseline HbA1c ranged from 8.1 to 8.6% (65 to 69 mmol/mol; Table 1).

Efficacy Measures

HbA1c was significantly reduced from baseline among all groups ($p < 0.001$; Table 2). FPG reductions were numerically greater for exenatide twice daily versus comparator in both studies in all BMI range groups except BMI <30 kg/m² in the placebo-controlled study. Baseline BMI was not correlated with changes from baseline in HbA1c (range of r-values, −0.05 to −0.15) or FPG (range of r-values, −0.04 to −0.13) for any treatment group in either study. Achievement of HbA1c <7.0% (<53 mmol/mol) was numerically higher for patients receiving add-on exenatide twice daily versus comparator in all groups

Table 2. Metabolic and cardiovascular characteristics in the intention-to-treat population.

Lispro-comparator study	Exenatide twice daily BMI<30 kg/m² n = 107	Exenatide twice daily BMI30–35 kg/m² n = 120	Exenatide twice daily BMI>35 kg/m² n = 88	Insulin lispro BMI<30 kg/m² n = 113	Insulin lispro BMI30–35 kg/m² n = 111	Insulin lispro BMI>35 kg/m² n = 88
Change from baseline						
HbA1c, mmol/mol	−10.7 (1.0)*	−10.9 (0.8)*	−11.9 (1.2)*	−9.6 (0.9)*	−11.0 (0.9)*	−12.4 (1.0)*
FPG, mmol/l	−0.22 (0.26)	−0.65 (0.27)*	−0.62 (0.33)	0.67 (0.28)*	0.22 (0.32)	−0.16 (0.34)
Body weight, kg	−2.1 (0.3)*	−2.0 (0.3)*	−3.6 (0.6)*	1.8 (0.3)*	1.5 (0.3)*	2.3 (0.5)*
SBP, mmHg	−4.3 (1.5)*	−4.0 (1.4)*	−5.3 (1.7)*	2.1 (1.6)	1.8 (1.3)	−1.4 (1.8)
DBP, mmHg	−0.2 (0.9)	−1.1 (0.8)	−1.9 (1.2)	1.3 (1.0)	0.6 (0.8)	−1.7 (1.0)
LDL cholesterol, mmol/l	−0.01 (0.07)	−0.11 (0.05)*	−0.16 (0.07)*	0.05 (0.06)	−0.01 (0.06)	−0.13 (0.08)
HDL cholesterol, mmol/l	−0.05 (0.02)*	−0.04 (0.02)*	−0.01 (0.02)	0.03 (0.02)	0.05 (0.02)*	0.03 (0.02)
LDL cholesterol/HDL cholesterol ratio, mmol/l	0.07 (0.06)	−0.04 (0.05)	−0.13 (0.06)*	0.01 (0.06)	−0.09 (0.06)	−0.15 (0.07)*
Total cholesterol, mmol/l	−0.09 (0.08)	−0.1 (0.06)	−0.16 (0.09)	0.09 (0.08)	0.05 (0.07)	−0.12 (0.09)
Triglycerides, mmol/l, median	−0.07	0.12	0.03	0.01	−0.05	−0.06
Patients achieving HbA1c <7.0% (<53 mmol/mol) at endpoint, n (%)	56 (52.3)	42 (35.0)	36 (40.9)	46 (40.7)	51 (45.9)	28 (31.8)
Patients achieving HbA1c <7.0% (<53 mmol/mol) and no weight gain at endpoint, n (%)	51 (47.7)	31 (25.8)	33 (37.5)	16 (14.2)	21 (18.9)	10 (11.4)

Placebo-controlled study	Exenatide twice daily BMI <30 kg/m² n = 36	Exenatide twice daily BMI 30–35 kg/m² n = 50	Exenatide twice daily BMI >35 kg/m² n = 51	Placebo BMI <30 kg/m² n = 43	Placebo BMI 30–35 kg/m² n = 35	Placebo BMI >35 kg/m² n = 44
Change from baseline						
HbA1c, mmol/mol	−12.5 (2.0)*	−16.5 (1.6)*	−16.5 (1.4)*	−9.6 (1.6)*	−9.8 (2.1)*	−11.9 (1.5)*
FPG, mmol/l	−0.32 (0.65)	−1.45 (0.39)*	−1.06 (0.49)*	−0.53 (0.45)	−0.77 (0.72)	−0.94 (0.65)
Body weight, kg	−0.4 (0.4)	−2.6 (0.6)*	−1.5 (0.6)*	1.2 (0.4)*	−0 (0.6)	1.2 (0.6)*
SBP, mmHg	−3.6 (2.5)	−2.8 (2.3)	−4.4 (1.9)*	1.2 (2.0)	1.6 (3.0)	−0.1 (2.6)
DBP, mmHg	−1.5 (1.0)	−2.1 (1.2)	−3.4 (1.3)*	3.0 (1.0)*	1.2 (1.6)	0.2 (1.4)
LDL cholesterol, mmol/l	0.0 (0.17)	−0.30 (0.10)*	−0.09 (0.10)	0.14 (0.10)	0.04 (0.10)	0.0 (0.11)
HDL cholesterol, mmol/l	−0.05 (0.03)	0 (0.02)	0.04 (0.01)*	−0.01 (0.09)	0 (0.03)	−0.01 (0.02)
LDL cholesterol/HDL cholesterol ratio, mmol/l	0.11 (0.15)	−0.31 (0.11)*	−0.13 (0.09)	0.13 (0.13)	0.05 (0.08)	−0.02 (0.12)
Total cholesterol, mmol/l	0.03 (0.18)	−0.28 (0.11)*	−0.08 (0.13)	0.14 (0.11)	0.08 (0.11)	−0.01 (0.12)
Triglycerides, mmol/l, median	0.10	−0.17	0.04	−0.02	−0.02	−0.04
Patients achieving HbA1c <7.0% (<53 mmol/mol) at endpoint, n (%)	16 (44.4)	33 (66.0)	25 (49.0)	11 (25.6)	10 (28.6)	13 (29.5)
Patients achieving HbA1c <7.0% (<53 mmol/mol) and no weight gain at endpoint, n (%)	10 (27.8)	25 (50.0)	20 (39.2)	5 (11.6)	8 (22.9)	8 (18.2)

Data are mean (standard error) unless otherwise stated. BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; SBP, systolic blood pressure.
*$p < 0.05$.

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except for the BMI 30–35 kg/m^2 group in the lispro-comparator study (Table 2).

Body weight was significantly reduced among patients receiving add-on exenatide twice daily across all groups except the <30 kg/m^2 BMI group in the placebo-controlled study ($p < 0.05$; Table 2). Increases in body weight were observed for both comparators. Baseline BMI was not correlated with changes from baseline in body weight for any treatment in either study (range of *r*-values, −0.18 to 0.09). Achievement of HbA1c <7.0% (<53 mmol/mol) and no weight gain was consistently higher for patients receiving exenatide twice daily versus comparator in both studies (Table 2).

When excluding patients who added on new antihypertensive medications (lispro-comparator study: exenatide twice daily, n = 2; insulin lispro, n = 5; placebo-controlled study: exenatide twice daily, n = 14; placebo, n = 14), the BP-lowering effect of add-on exenatide twice daily remained and changes in BP observed were similar to those in the overall ITT populations of the BMI range groups (Table 2). Baseline BMI was not correlated with changes from baseline in SBP (range of *r*-values, −0.03 to −0.11) or diastolic BP (range of *r*-values, −0.08 to −0.14) for any treatment in either study.

None of the patients in the lispro-comparator study added on new lipid-lowering medications after randomization. In the placebo-controlled study, 10 patients receiving exenatide twice daily and zero placebo-treated patients added on lipid-lowering medications. When excluding these patients, the changes from baseline in LDL cholesterol, HDL cholesterol and total cholesterol were similar to those in the overall ITT population of each BMI range group. Baseline BMI was not correlated with changes in LDL cholesterol, HDL cholesterol, total cholesterol, or triglycerides for any treatment in either study (range of *r*-values for all lipids, −0.14 to 0.24).

Safety and Tolerability

Rates of minor hypoglycaemia were numerically lower among patients receiving add-on exenatide twice daily versus add-on insulin lispro in all BMI range groups in the lispro-comparator study and versus placebo in the lowest BMI range groups in the placebo-controlled study (Table S1, Supporting Information). Major hypoglycaemia was infrequent and occurred in a smaller proportion of patients receiving exenatide twice daily versus insulin lispro in the lispro-comparator study; major hypoglycaemia was not reported in the placebo-controlled study for exenatide twice daily. The most frequent TEAEs (≥10% incidence) by preferred term included diarrhoea, nausea, vomiting and nasopharyngitis in the lispro-comparator study, and nausea, diarrhoea and vomiting in the placebo-controlled study.

Discussion

In this secondary analysis of two clinical trials in which patients with T2D were randomized to add-on exenatide twice daily versus add-on insulin lispro or placebo, while taking background insulin glargine with or without metformin and/or pioglitazone, baseline BMI was not correlated with changes from baseline in the efficacy variables evaluated. In both studies, exenatide twice daily was associated with significant reductions in HbA1c and body weight. In the lispro-comparator study, HbA1c reductions were equivalent for exenatide twice daily and insulin lispro; however, insulin lispro was associated with significant weight gain. Thus, the decision by some European national authorities or health insurance companies to restrict GLP-1RA reimbursement to patients with BMI >35 kg/m^2 is not consistent with medical evidence.

Other studies of exenatide twice daily have also found similar efficacy across BMI subgroups. In *post hoc* analyses of exenatide twice daily (16 randomized controlled trials), HbA1c, body weight and SBP reductions were significant for all BMI range groups ($p < 0.0001$) [10,11]. Similarly, studies with liraglutide [12] and lixisenatide added on to basal insulin [13] have reported reductions in HbA1c and body weight across BMI range groups. These effects appear to complement the guideline-recommended management of cardiovascular risk factors.

Hypoglycaemia is a concern in patients with T2D taking both basal and mealtime insulins [14,15], and exenatide twice daily added to background insulin glargine appeared to mitigate this risk. The trend of fewer minor hypoglycaemic events in patients with BMI <30 kg/m^2 receiving exenatide twice daily treatment versus comparators in both studies is important because low BMI (25 vs 35 kg/m^2) is associated with increased non-severe hypoglycaemia risk in patients with T2D [16]. In both studies and for all BMI range groups, exenatide twice daily treatment was associated with an increased rate of gastrointestinal TEAEs versus comparator.

Limitations of the present analysis include differences in study design, the retrospective nature of the analysis, and the lack of balance across BMI range groups.

In conclusion, recent international guidelines have adopted a more favourable opinion on the combination of basal insulin and GLP-1RAs after basal insulin failure. Exenatide twice daily effectively reduced HbA1c and body weight across BMI range groups, including patients with near-normal BMI, and was well tolerated with a low risk of hypoglycaemia. Changes in efficacy variables were not significantly correlated with baseline BMI. There is evidence of clinically meaningful glycaemic and weight benefits from the addition of exenatide twice daily to insulin glargine in both patients of normal weight and patients with mild to severe obesity, and there does not appear to be a threshold below which exenatide twice daily is not effective. Limiting reimbursement to patients with obesity (BMI >35 kg/m^2) may result in the undertreatment of patients with lower BMI and may increase their risk of hypoglycaemia and unwanted weight gain.

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Conflict of Interest

B. H. R. W. has received grant support for clinical studies and also consulting fees for serving on advisory boards and has served as a speaker for AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Novo Nordisk, Pfizer and Sanofi Aventis. He has also received consulting fees from Eli Lilly and Company as a member of the 4B Study and of the DURABLE Trial Data Monitoring Committee, and grant support from the European Union (BBMRI, BioSHaRE, and MDS-Right Consortiums), JDRF and Diabetes Fonds Nederland. L. V. G. is/has been a member of the advisory boards and speakers' bureaus for AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, Janssen, Johnson & Johnson, Merck MSD, Novo Nordisk and Sanofi (2011–2013). He also received grant support from the European Union (Hepadip & Resolve Consortium) and National Research Funds, Belgium. S. D. G. has received grant support for clinical studies from AstraZeneca, Eli Lilly and Company, GlaxoSmithKline, Intarcia, Lexicon, Novo Nordisk, Pfizer, Servier, and Takeda. J. H. has received consulting fees for statistical consulting.

B. H. R. W. and L. V. G. were investigators in the 4B Study Group, B. H. R. W., L. V. G., S. D. G. and J. H. conceived the analysis and participated in the writing of the manuscript. All authors approved the final version of the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study design.

Table S1. Treatment-emergent adverse events occurring in ≥10% of patients in any group and hypoglycaemic events, according to baseline body mass index range group (intent-to-treat population).

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